REMARKS

Currently pending claims 1-17 are rejected as being indefinite or as anticipated by or obvious over certain prior art references. These rejections are respectfully traversed for the reasons given below and reconsideration is requested.

The Applicants appreciate the Examiner's summary that:

1) The Applicants' amendments filed 17 January 2008 and new claim 17 have been acknowledged and entered;

2) The rejections of claims 1-16 under 35 U.S.C § 112, first paragraph, have been withdrawn;

3) The rejection of claim 5 under 35 U.S.C § 112, first paragraph, has been withdrawn; and

4) The rejection of claim 4 under 35 U.S.C § 112, second paragraph, has been withdrawn.

The Applicants also acknowledge that the Examiner states at p. 2 that he has not considered the Declaration of Mary Jo Ondrechen filed 17 January 2008, as the Declaration as submitted was not signed. Although the Declaration appears now to be moot as the rejections that it was being submitted to overcome have been withdrawn, for completeness of the record, the signed Declaration as filed on 17 January 2008 is submitted herewith.

Also submitted is a new Declaration of Mary Jo Ondrechen, which is directed to answering the newly recited rejections.

Rejection under 35 USC § 112, second paragraph, for Indefiniteness

Claims 1-17 are newly rejected as indefinite. Claim 1 is rejected for reciting "said interaction sites determination" in line 11 without sufficient antecedent basis. Claim 1 has now been amended to read, at line 11, "displaying said putative interaction sites," which language parallels that used in the limitation at lines 9-10. Thus, Applicants submit that the rejection has been overcome.

Claim 11 has been rejected as indefinite for using the term "wide" in line 3, the Examiner stating that "wide" is a relative term, not supported by a standard. The Examiner has amended claim 11 to recite: "The method of claim 2, wherein said perturbed titration curve is an elongated titration curve 'having a non-sigmoidal shape.'" The new language (in quotations) is supported in the specification at least at p. 7, line 28 - p. 8, line 4. The Applicants submit that the new language is definite in meaning and the rejection is overcome.

Rejection under 35 USC § 102, for Anticipation

Claims 1-3, 5 and 11-13 have been rejected as being anticipated by Beroza et al. This rejection is respectfully traversed. The accompanying Declaration of co-inventor Mary Jo Ondrechen signed August 14, 2008, is referenced in the following discussion of the differences between the teachings of Beroza et al. and the claimed invention.

As recited above, claim 1 as amended is directed to:

> A method for determining interaction sites in a protein having an identified three-dimensional structure, said method comprising the steps of:
> 1) providing an identified three-dimensional structure for said protein;
> 2) identifying, in said protein structure, ionizable amino acid residues having anomalous predicted theoretical microscopic titration curve behavior;
> 3) clustering certain of said identified ionizable amino acid residues into putative interaction sites; and
> 4) displaying said putative interaction sites.

At pp. 5-6 of the Office Action, it appears that the Examiner is trying to "force fit" the teachings of the reference into the language of the Applicants' claims. In the first paragraph on p. 5, the Examiner states that Beroza et al. teaches at Figure 3 identifying ionizable amino acid residues with anomalous predicted titration curves and then clustering those residues into a putative interaction site. However, Figure 3 shows that Beroza *starts* with the reactive sites, Q_A and Q_B, and then *identifies* the residues of interest around the quinones *using displayed information*, not the other way around as required by claim 1 and the claims dependent thereon.

Furthermore, as the Ondrechen Declaration of August 14, 2008 points out in paragraphs 8 and 9, while there may be three residues with perturbed theoretical titration curves near Q_B (Fig. 3B), there is only one such residue near Q_A, not a "cluster" as required by the Applicants' claims. In addition, as pointed out in the latter part of paragraph 9 of the Declaration, there is absolutely no information given in Beroza et al. about any of the other reactive parts of the photosynthetic reaction center protein or about any other protein other than the photosynthetic reaction center. There is nothing to indicate that this supposed "phenomenon" could be general. If a cluster of residues with perturbed theoretical titration curves is observed in this one part of the photosynthetic reaction center, but no such phenomena are reported for the other reactive parts of the photosynthetic reaction center, how could this indicate to one of ordinary skill that he or she could use this information to *identify* reactive areas inside a protein, in the manner claimed in the instant application?

The Examiner's rejection of claim 2, second paragraph of p. 5, does not even make a *prima facia* case for anticipation. For example, step b) of claim 2 recites "calculating a titration curve for *each ionizable residue in said protein*" and step c) recites "evaluating the shape of said titration curve *for each said residue.*" Neither step is even suggested by the Examiner as being taught in Beroza et al.

Claim 3 recites: The method of claim 2, further comprising the step of identifying any said perturbed titration curve residues that *do not fall* into any said cluster, in other words, those that are not part of a putative active site. In contrast, as the Examiner points out in the final paragraph on p. 5, Beroza et al. "eliminates" Asp L213 from the cluster in which it *appears to fall.* Thus, Beroza eliminates a valid datum point for a residue that does not fit the theory rather than teaching Applicants' claim 3.

In regard to the rejections of claims 5 and 11-13, Applicants submit that whatever is taught in Beroza et al. at the additional places cited by the Examiner does not make up for the previously described deficiencies and the rejections for anticipation are overcome.

Rejection under 35 USC § 103(a), for Obviousness

Claims 4 and 17 are rejected for obviousness over Beroza et al. in combination, respectively, with Guex et al. or Baker et al. Applicants submit that a combination of Beroza et al. with either or both of the secondary references still would not overcome the deficiencies of the primary reference, Beroza et al. itself, as recited above, and the rejections are overcome.

In summary, Applicants submit, as pointed out in various places in the Ondrechen Declaration, the information in the Beroza et al. paper would not lead one of ordinary skill to the conclusion that one could relate the information described to any other protein and *predict* active sites from observed anomalies in the shapes of computed titration curves. In fact, because the photosynthetic reaction center is so special, one of ordinary skill might instead conclude that the reported titration behavior is *actually unique* to one particular, local area inside the photosynthetic reaction center.

The Beroza paper also indicates that the active residues in the photosynthetic reaction center have shifted pK_as. Based on the information provided in Figures 3A and 3B, it might appear that shifted pK_as are a better predictor of reactive zones than are the disturbed predicted titration curve shapes. The Applicants have found this not to be the case, as discussed in the Ondrechen Declaration. In order to be useful to identify active sites, an observed phenomenon has to be highly prevalent in active sites and also uncommon elsewhere in the protein structure. There is nothing in the Beroza paper to suggest either of these conditions.

The Applicants submit that all claims in the application are in condition for allowance and such action is requested.

The Examiner is encouraged to telephone the undersigned attorney to discuss any matter that would expedite allowance of the present application.

Respectfully submitted,

MARY JO ONDRECHEN ET AL.

By: Holliday C. Heine
Holliday C. Heine, Ph.D.
Registration No. 34,346
Attorney for Applicant(s)

WEINGARTEN, SCHURGIN,
GAGNEBIN & LEBOVICI LLP
Ten Post Office Square
Boston, MA 02109
Telephone: (617) 542-2290
Telecopier: (617) 451-0313

HCH/dvm/370437.1